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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/990,438	11/14/2001	David Botstein	10466/201	2374

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EXAMINER	
KAUFMAN, CLAIRE M	
ART UNIT	**PAPER NUMBER**
1646	

DATE MAILED: 10/18/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/990,438	BOTSTEIN ET AL.	
	Examiner	Art Unit	
	Claire M. Kaufman	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 July 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *124,125 and 129-131* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *124,125 and 129-131* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/31/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicants' submission filed on 7/31/06 has been entered.

Response to Amendments

The second Declaration of Dr. Paul Polakis filed under 37 CFR 1.132 filed 7/31/06 is insufficient to overcome the rejection of claims based upon 35 USC 101 and 112, first paragraph, as set forth in the last Office action because: While statements are made in the Polakis Declaration concerning correspondence of mRNA expression and corresponding encoded polypeptide expression in particular cell types, there remain issues about the correspondence tied to genomic DNA and encoded protein correlation, insufficiency of disclosure in the instant specification as well as the impact of recent proteomic and transcriptiomic research findings discussed in the previous Office action and below.

The first 37 CFR 1.132 declaration of Dr. Polakis (resubmitted 7/31/06) was filed 8/20/04 and previously considered and found insufficient to overcome the rejections for the reasons set forth in the previous Office action.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 101

Claims 124-125 and 129-131 remain rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility for the reasons set forth in the previous Office action.

Applicants argue (pages 3-4) that there is no legal requirement for a "necessary" correlation between increase in gene amplification and protein expression, but instead a

preponderance of evidence or, in other words, that is more likely than not the person of ordinary skill in the art would reasonably expect a correlation. The argument has been fully considered, but is not persuasive. Applicants have submitted 149 references to support the argument for correlation of gene copy number and protein level. However, among the articles only Ornitoft et al. (originally cited 11/09/04) and Godbout et al. (submitted as an abstract, #30, which will be addressed below) are pertinent to the issue at hand: does gene copy number correlate with protein expression. This issue is not whether mRNA correlates with protein level, which is the issue that all the other articles deal with and will not be focused on here. The reason is described in the textbook by Lewin (Gene VI, 1997, #141 cited by Applicants 7/31/06, sentence bridging pages 847-848), who states that, "[H]aving acknowledged that control of gene expression can occur at multiple stages, and that production of RNA cannot inevitably be equated with production of protein, it is clear that the overwhelming majority of regulatory events occur at the initiation of transcription."

Applicants argue (bottom of p. 6) that Ornitoft et al. show that for the majority of genes, mRNA and protein levels correlate, citing a correlation coefficient of $p<0.005$ with only 1/40 not correlating (paragraph bridging pages 17-18 of response). The argument has been considered. While the general interpretation of Ornitoft et al. is correct the facts are not. Upon reading the full paragraph bridging pages 42-43 of Ornitoft et al., one can see that for TCC pair 827/532, mRNA levels did not correlate with protein levels for one gene; however, for group TCC 733 and 335, 7 of 26 did not correlate. Therefore, for the 40 total pairs shown in Fig. 4, 8/40 did not have correlating mRNA and protein levels. While the majority did correlate, it was 8/40 instead of 1/40 that did not. Ornitoft et al. (p. 40, col. 2, second paragraph) found that, "In most cases, chromosomal gains detected by CGH were accompanied by an increased level of transcripts in both TCCs 733 (77%) and 827 (80%) (Table I, top). Chromosomal losses, on the other hand, were not accompanied by decreased expression in several cases, and were often registered as having unaltered RNA levels (Table I, top). The inability to detect RNA expression changes in these cases was not because of fewer genes mapping to the lost regions (data not shown)." They go on to say that detection was very limited. Further, the data do not look at a 1:1 correspondence of genomic DNA and the mRNA which is transcribed from it. It looks at gene clusters in chromosomal regions. Therefore, the results of Ornitoft et al. are not directly

applicable to the instant situation for PRO290.

Applicants argue (page 4) that the declarations by Dr. Polakis are pertinent to the instant rejection and are based on factual findings. The declarations support the argument that mRNA levels are predictive of protein levels and that PRO290 mRNA is significantly overexpressed in tumor compared to a normal control. The argument has been fully considered, but is not persuasive. Again, the issue at hand is not the correlation of mRNA to protein level but of genomic DNA copy number. However, for completeness of record, it should be pointed out that the second declaration refers to a chart without objective information about staining intensity. Nor is it clear how the mRNA levels were analyzed, *i.e.*, by RT-PCR, microarray, Northern Blot, *etc.* Only Dr. Polakis' conclusions are provided in the declarations. The first and second declarations of Dr. Polakis were considered, as were the quoted statements' relationship to relevant art. While the opinions of Dr. Polakis have been considered, they are not found persuasive to overcome the rejection of the claimed invention under 35 USC 101 or 112, first paragraph, enablement for the reasons of record and for the reasons that they do not address the correspondence of genomic DNA levels to protein levels.

Applicants maintain (top of p. 4) that Pennica et al. and Konopka et al. do not show a lack of correlation between DNA amplification and elevated protein levels in general. For the reasons discussed in the previous Office action (p. 5 and 15-16), these references are pertinent to the lack of reasonable expectation that for any given gene the level of gene copy number will correlate with protein expression.

While the vast majority of newly cited references are drawn to predictability of protein on the basis of mRNA amplification (and for reasons cited above do not merit further discussion), Godbout et al. is pertinent to the issue at hand. However, the Examiner finds Applicants interpretation of the reference to be erroneous. Far from teaching predictability for expression of PRO290 on the basis of a minor genomic amplification, the abstract of Godbout et al. teaches "The DEAD box gene, DDX1, is a putative RNA helicase that is co-amplified with MYCN in a subset of retinoblastoma (RB) and neuroblastoma (NB) tumors and cell lines. Although gene amplification usually involves hundreds to thousands of kilobase pairs of DNA, a number of studies suggest that co-amplified genes are only overexpressed if they provide a selective advantage to the cells in which they are amplified." The protein encoded by the DDX gene had

been characterized as being a putative RNA helicase, a type of enzyme that would be expected to confer a selective advantage to the cells in which it (the DDX gene) was amplified. On page 21167, right column, first full paragraph, Godbout et al. state:

> It is generally accepted that co-amplified genes are not over-expressed unless they provide a selective growth advantage to the cell (48, 49)." For example, although ERBA is closely linked to ERBB2 in breast cancer and both genes are commonly amplified in these tumors, ERBA is not overexpressed (48). Similarly, three genes mapping to 12q13-14 (CDK4, SAS and MDM2) are overexpressed in a high percentage of malignant gliomas showing amplification of this chromosomal region, while other genes mapping to this region (GADD153, GL1, and A2MR) are rarely overexpressed in gene-amplified malignant gliomas (50, 51). The first three genes are probably the main targets of the amplification process, while the latter three genes are probably incidentally included in the amplicons.

On the contrary, there is no structure/function analysis in the specification regarding the putative protein encoded by the PRO290 gene. It is not disclosed, and based upon the sequence searches in this case the Examiner can not find any reason to suspect, that the protein encoded by the PRO290 gene would confer any selective advantage on a cell expressing it. It has no known homology to an RNA helicase or any other protein that would be expected to confer a selective advantage to a tumor cell. Further, it could not be determined whether the level of genomic amplification of the DDX1 gene was comparable to that disclosed for PRO290.

In summary, of the tens of new articles submitted, only a single one, Godbout et al., is drawn to the predictability of protein levels based upon genomic DNA amplification of an individual gene; and, that one supports the Examiner's assertion that it is more likely than not that the PRO290 protein would *not* be expected to be found in increased amounts in the cells tested by Applicants, and thus has no utility as a cancer diagnostic.

An additional reference that provides evidence that gene amplification does not necessarily lead to increased transcript is Li et al., Oncogene, Vol. 25, pages 2628-2635, 2006. Li et al. used a functional approach that integrated simultaneous genomic and transcript microarray, proteomics, and tissue microarray analyses to directly identify putative oncogenes in lung adenocarcinoma. On page 2633, paragraph beginning at the bottom of col. 1, Li et al. state:

> Although the main focus of this study was to specifically identify putative oncogenes, it should be noted that 90.7% of the genes showing high protein

> expression did not show corresponding increases in both DNA copy number and transcript, a finding consistent with that of others that transcriptional, translational, and post-translational regulatory mechanisms can greately influence the abundance of portein in lung tumorigenesis (Chen *et al.*, 2002).... In our study, 68.8% of the genes showing over-representation in the genome did not show elevated transcript levels, implying that at least some of these genes are 'passenger' genes that are concurrently amplified because of their location with respect to amplicons but lack biological relevance in terms of the development of lung adenocarcinoma.

While the Examiner has the resources to cite only a handful of references showing the unpredictability of a correlation between genomic DNA and protein levels, these references stand to show that one cannot make assumptions about the use of PRO290 polypeptide in view of the methods used and information provided in the instant specification.

Conclusion

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Applicants are advised that the instant rejection is made final because the same claims were maintained as rejected on the same grounds that have been of record. However, a new reference has been cited as evidence supporting the rejections of record.. Applicants may submit counter-evidence in response to this office action, which will be appropriately entered after final. Alternatively, Applicants may wish to submit an Appeal Brief in response to this office action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Claire M. Kaufman, whose telephone number is (571) 272-0873. Dr. Kaufman can generally be reached Monday, Tuesday, Thursday and Friday from 9:30AM to 2:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, can be reached at (571) 272-0835.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Official papers filed by fax should be directed to (571) 273-8300. NOTE: If applicant *does* submit a paper by fax, the original signed copy should be retained by the applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Claire M. Kaufman, Ph.D.
Patent Examiner, Art Unit 1646
October 10, 2006

LORRAINE SPECTOR
PRIMARY EXAMINER